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REVIEW

Acute Myeloid Leukemia in the Elderly Patient: New Strategies

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ABSTRACT

Although selected older adults with acute myeloid leukemia can benefit from intensive therapies, recent evidences support the use of lower-intensity therapies (hypomethylating agents or low-dose cytarabine) in most of these patients and emphasize the importance of tolerability and quality of life. Individualized approaches to treatment decision-making beyond consideration of chronologic age alone should therefore be considered. One promising strategy is to combine low-intensity treatments with novel agents.

Keywords: Acute myeloid leukemia; Chemotherapy; Elderly; Hypomethylating agents; Supportive care; Targeted therapy

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INTRODUCTION

Acute myeloid leukemia (AML) occurs mainly in patients aged 65 years or older. Median age at diagnosis ranges between 68 and 72 years, with approximately one-third of patients aged 75 years or older [1]. There is currently no consensus regarding optimal therapeutic strategy for older adults with AML, who are generally defined as those aged 60 years or older [2, 3]. Intensive chemotherapy has demonstrated a survival advantage over supportive care [2]. However, due to comorbid conditions and disease features, concerns regarding efficacy and toxicity have resulted in the ineligibility of many older patients with AML for this type of treatment [4]. Prognostic models have been developed to determine which older adults are likely to benefit from specific therapies [5–7]. However, these algorithms are not always easily applicable in daily clinical practice and each model relies on chronological age as a surrogate for measurable patient-specific factors that vary among individuals of similar age. Furthermore, even in patients who can tolerate intensive therapy, outcomes remain poor. Recently published single-center data

showed a complete remission (CR) rate of 48% after intensive chemotherapy, with median overall survival of 7.4 months and 5-year overall survival of only 10% [8]. Over the last decades, there has been little progress in improving prognosis for patients aged 60 years or older, resulting in unmet needs necessitating novel therapeutic strategies [9].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

AGING AND AML

Acute myeloid leukemia (AML) is a different disease in older patients. Aging is a complex process influenced by genetic variables as well as environmental factors [10]. Leukemia cells are more likely to be $CD34^{+}CD33^{+}$ which correlates with poor outcome [11], to have more poor-risk karyotypes [complex karyotypes, chromosome 3 abnormalities, abnormalities of 11q, total or partial monosomy 7, total or partial monosomy 5] and fewer favorable-risk cytogenetics [t(8;21), inv(16) or t(16;16), or t(15;17)] [12]. Older patients have shown a higher probability of RAS (Rat sarcoma), SRC (Sarcoma), and tumor necrosis factor pathway activation than younger patients, which may contribute to their poorer survival [13]. Leukemia blasts have higher expression of the *MRD1* gene, responsible for drug efflux and resistance [14], and are less likely to undergo apoptosis [15]. Poor outcome in older patients with AML is also correlated with impaired functional and nutritional status, presence of comorbidities, and mental health leading to loss of autonomy after chemotherapy [16–18].

INTENSIVE THERAPY IN ELDERLY PATIENTS WITH AML

Despite recent improvements, median survival in clinical trials using intensive chemotherapy remains less than 1 year [19]. Although older patients enrolled in clinical trials have adequate performance status, they are less likely than younger adults to achieve CR and remain relapse-free. Inversely, early death rate is higher [19, 20]. Standard induction chemotherapy remains a combination of intermediate-dose cytarabine with an anthracycline administered for 7 and 3 days ('7 + 3'), respectively. This approach has been shown to improve survival as compared with supportive care only [21]. Different induction regimens (including anthracycline substitution, addition of hematopoietic growth factors, modulation of multidrug resistance, or addition of a novel agent) have been proposed but have not consistently improved efficacy (reviewed in [17]). However, improved outcomes have been reported in a subset of patients aged 60–65 years receiving higher dose of daunorubicin (90 mg/m^2) when compared to a dosage of 45 mg/m^2 [22], but this was not true if compared to the dosage of 60 mg/m^2 [23]. Improved outcomes have also been reported in patients receiving low-dose gemtuzumab ozogamicin combined with a standard induction chemotherapy [24, 25]. CPX-351, a liposomal formulation of a synergistic 5:1 molar ratio of cytarabine and daunorubicin, was studied in a randomized phase 2 trial in older patients with AML and showed improved survival for CPX-351 compared with '7 + 3' chemotherapy [26]. Optimal duration or intensity of consolidation therapy in older patients remains unclear, although an association has been established between dose-intensity and increased toxicity [27]. Overall, up

to 20% of older adults who achieved CR, enrolled in intensive chemotherapy trials, do not receive any consolidation therapy. Several studies have indicated that subsequent cycles of intensive chemotherapy following achievement of CR offered no benefit to patients [27, 28]. The introduction of reduced-intensity conditioning regimens has resulted to an increased use of hematopoietic stem cell transplantation (HSCT) in patients aged 60–70 years. Although HSCT appears feasible for selected patients, it remains unclear whether this procedure is better than more conventional approaches in terms of survival and quality of life [29, 30]. However, analyses of the SEER database clearly show longer overall survival in patients who received allogeneic HSCT [4].

FITNESS AND INTENSIVE CARE ELIGIBLITY

Older patients with favorable prognostic AML (acute promyelocytic leukemia, core binding factor AML, and *NPM1*-mutated AML) can be cured with intensive chemotherapy [2, 31]. Therefore, the issue is to identify the elderly patients with AML who could benefit from intensive chemotherapy. Prognostic models have been developed from clinical trial data to improve outcome prediction for older patients with AML [3, 5–7]. Each of these algorithms provides useful information, but primarily explores the heterogeneity of tumor biology and relies on chronological age as a surrogate for measurable patient-specific factors. The one most consistent factor with clinical outcome after intensive chemotherapy was cytogenetics. Poor performance status can be related to the disease itself and should not be considered as a limiting factor for intensive chemotherapy. In multivariate analyses, poor outcome or early death were significantly correlated with poor cytogenetic and not with age or comorbidities [32]. Older patients with AML, particularly those older than age 70 years, have specific needs. The traditional oncology evaluation is often not adequate and will fail to uncover specific problems. Therefore, there has been increasing debate regarding the appropriate therapeutic decision-making for the geriatric patient population, which should be offered therapy to prolong both survival and quality of life. Clinical tools have been developed to predict grade 3–4 chemotherapy toxicity [33]. The chemotherapy risk assessment scale for high-age patients (CRASH) score can distinguish several risk levels of severe chemotherapy toxicity [34] and should be incorporated into clinical trials.

HYPOMETHYLATING AGENTS IN ELDERLY PATIENTS WITH AML

For many older patients, the risk of treatment-related mortality may outweigh the potential transient benefits of intensive chemotherapy. Lower-intensity regimens have then been proposed. In this setting, low-dose cytarabine has demonstrated improved survival among patients considered not fit for intensive treatment compared with supportive care alone, and is usually regarded as the standard therapy for this type of patient, although fitness has not clearly been defined [35]. However, outcomes with low-dose cytarabine are generally poor with a median survival time of only 4 months. Recent studies have shown that gene hypermethylation is widespread in patients with AML and is implicated in leukemogenesis [36]. Hypomethylating agents (decitabine and azacitidine) may have the potential to improve survival and quality of

life in elderly patients and have been assessed in phase 3 studies [37–39]. The DACO-016 study (ClinicalTrials.gov number, NCT00260832) has compared the efficacy and safety of decitabine (20 mg/m^2/day for 5 days every 4 weeks) versus best supportive care or low-dose cytarabine (20 mg/m^2/day for 10 days every 4 weeks) in 485 patients ineligible for intensive chemotherapy [37]. While the first analysis demonstrated a non-significant trend towards improved overall survival in the decitabine arm, an unplanned ad hoc analysis performed 1 year later following 446 deaths showed a significant difference between the two arms of randomization (median overall survival: 7.7 versus 5 months; $P = 0.037$) [37]. Following this trial, decitabine was approved by the European Medicines Agency (EMA) for the treatment of AML in patients aged 65 years or older who are not candidates for intensive chemotherapy, but not by the US Food and Drug Agency (FDA). The AZA-001 trial (ClinicalTrials.gov number, NCT00071799) compared the efficacy and safety of azacitidine with conventional care regimens (best supportive care, low-dose cytarabine, intensive chemotherapy) in 358 patients with predominantly intermediate-2/high-risk myelodysplastic syndromes [38]. However, 113 patients of this series were with AML, when considering the World Health Organization (WHO) classification (20–30% blasts). In these patients, a significant difference in overall survival favoring azacitidine versus conventional care regimens was detected (median overall survival: 24.5 versus 16.0 months; $P = 0.005$). Furthermore, more patients transfusion-dependent at baseline achieved transfusion independence with azacitidine (41% versus 18%; $P = 0.04$). Based on this analysis, azacitidine has become established as a treatment option for patients with 20–30% leukemia cells in bone marrow, who are ineligible for intensive chemotherapy. In the AZA-AML-001 trial (ClinicalTrials.gov number, NCT01074047), 480 patients with more than 30% leukemia cells in bone marrow were randomized to receive either azacitidine (75 mg/m^2/day for 7 days every 4 weeks) or conventional care regimens [39]. Median overall survival was 10.4 months in the azacitidine arm compared to 6.5 months in the conventional care regimens group ($P = 0.08$). However, when censoring patients at the start of the subsequent AML therapy, the analysis showed a longer median overall survival in patients receiving azacitidine (median overall survival: 12.1 months versus 6.9 months; $P = 0.019$) [39]. SGI-110, a dinucleotide of decitabine and deoxyguanosine with distinctive pharmacokinetic properties that allow a longer half-life and more extended decitabine exposure, is currently being investigated in older patients with AML. Response rate was 53% in a phase 2 first-line therapy in older patients with AML [40].

NOVEL TREATMENTS IN DEVELOPMENT FOR AML

Novel agents used as single-agent or in combination (Table 1) are under investigation for the treatment older patients with newly diagnosed AML. The anti-CD33-conjugated cytotoxic gemtuzumab ozogamicin, the nucleoside analogue prodrug clofarabine, and the farnesyltransferase inhibitor tipifarnib were both investigated in combination with low-dose cytarabine in a 'pick-a-winner' trial design. Combined data of gemtuzumab ozogamicin plus low-dose cytarabine demonstrated an improved response rate compared with low-

Table 1 Main ongoing randomized clinical trials with novel agents in development for older unfit patients with newly diagnosed acute myeloid leukemia

Novel agent	Mechanism of action	Combination	Comparator	Trial (clinicaltrials.gov number)
Barasertib	Aurora B kinase inhibitor	LD-AraC	Barasertib LD-AraC	Phase 2/3 (NCT00952588)
Bortezomib	Proteasome inhibitor	Decitabine	Decitabine	Phase 2 (NCT01420926)
Clofarabine	Nucleoside analogue prodrug	LD-AraC	Clofarabine	Phase 2 (NCT00088218)
ERY001	L-asparaginase encapsulated in red blood cells	LD-AraC	LD-AraC	Phase 2 (NCT01810705)
Gemtuzumab ozogamicin	Anti-CD33 conjugated with calicheamicin	LD-AraC	LD-AraC	Phase 3 (NCT00005823)
Gemtuzumab ozogamicin	Anti-CD33 conjugated with calicheamicin	LD-AraC	LD-AraC	Phase 2/3 (NCT00454480)
Lenalidomide	Immunomodulatory, anti-angiogenic, cytotoxicity	Azacitidine	Azacitidine, Lenalidomide	Phase 2 (NCT01358734)
Sapacitabine	Nucleoside analogue prodrug	Decitabine	Decitabine	Phase 3 (NCT01303796)
Tipifarnib	Farnesyltransferase inhibitor	LD-AraC	LD-AraC	Phase 2/3 (NCT00454480)
Tosedostat	Aminopeptidase inhibitor	Decitabine	Tosedostat + AraC	Phase 2 (NCT01567059)
Volasertib	Polo-like kinase inhibitor	LD-AraC	Placebo + LD-AraC	Phase 3 (NCT01721876)

LD-AraC low-dose cytosine arabinoside

dose cytarabine alone (30% versus 17%; $P = 0.006$), but no difference in terms of overall survival [41]. A comparison of clofarabine versus low-dose cytarabine also showed a higher response rate with clofarabine, but no difference in overall survival [42], while the addition of tipifarnib to low-dose cytarabine was found to have no effect on response or survival [43]. In combination with low-dose cytarabine compared with single-agent clofarabine, CR rate was higher in the first group (67% versus 31%; $P = 0.012$). Median overall survival was 11.4 months versus 5.8 months ($P = 0.10$), while median event-free survival was 7.1 versus 1.7 months ($P = 0.04$) [44]. In combination with azacitidine, gemtuzumab ozogamicin CR rates of 44% and 35% for patients with good-risk or poor-risk AML, respectively [45]. Sapacitabine, a nucleoside analogue prodrug, is currently under investigation in combination with decitabine (ClinicialTrials.gov number, NCT01303796). Preliminary data demonstrated response in 9/25 patients aged ≥70 years with newly diagnosed AML [46]. Volasertib, a cell cycle kinase inhibitor, is currently under phase 3 investigation in combination with low-dose cytarabine versus low-dose cytarabine alone (ClinicalTrials.gov number, NCT01721876). In a phase 2, volasertib plus low-dose cytarabine has shown improved efficacy versus low-dose cytarabine with CR rates of 31% versus 13% ($P = 0.05$). Median overall survival was also prolonged (8 versus 5.2 months; $P = 0.047$) [47]. The aurora kinase B inhibitor barasertib is under investigation in combination with low-dose cytarabine (ClincalTrials.gov number, NCT00952588). Phase 1 evaluation of this combination showed a response rate of 45% [48]. While the first part of the phase 3 trial has been reported [49], the clinical development of barasertib in AML has been discontinued. A clinical trial combining lenalidomide plus azacitidine is currently recruiting patients (ClinicalTrials.gov number, NCT01358734). A phase 1/2 with this combination showed 41% of CR, and a median overall survival of 20 weeks [50]. Vorinostat in combination with azacitidine is currently under investigation (ClinicalTrials.gov number, NCT00948064). Although not limited to older patients, available data from phase 2 showed 30% of CR and 7 months of median overall survival with this combination [51]. Two trials evaluating decitabine combinations are ongoing: One with tosedostat, an aminopeptidase inhibitor (ClinicalTrials.gov number, NCT01567059) and one with bordezomib, a proteasome inhibitor (ClinicalTrials.gov number, NCT01420926). Preliminary data with this last combination demonstrated 50% of response [52]. Older patients with *FLT3* mutant AML should ideally be considered for therapy incorporating a *FLT3* inhibitor. The addition of sorafenib, an oral inhibitor of multiple tyrosine kinases including *FLT3*, to upfront intensive chemotherapy was not beneficial [53]. However, a phase 2 trial of sorafenib combined with azacitidine in *FLT3* mutant AML of all ages resulted in an overall response rate of 46% [54]. Based on the discovery of recurrent somatic point mutations in the isocitrate dehydrogenase (*IDH1*) gene, and its isoform *IDH2*, small molecule inhibitors are being developed to inhibit the neomorphic enzyme, which activity results in the accumulation of the metabolite 2-hydroxyglutarate. Preliminary results of a phase 1 dose-escalation study with AG-221, an oral IDH2 inhibitor, showed good tolerance and no-limiting toxicities [55]. The tandem bromodomain (BRD)-containing family of transcriptional regulators, known as

bromodomains and extraterminal (BET) proteins, has emerged as major epigenetic regulators of proliferation and differentiation. In AML, the inhibition of BRD4 led to cell cycle arrest and apoptosis. A phase 1 clinical trial using the inhibitor OTX015 is currently ongoing [56].

PERSPECTIVES, UNRESOLVED ISSUES, AND CONCLUSIONS

Treatment recommendations for elderly patients with AML need to be individualized. Hypomethylating agents may provide an exciting new approach to the treatment of elderly patients potentially as monotherapy, and mainly in combination regimens with other agents. Although CR rate was higher with intensive chemotherapy, there was a trend for lower early mortality with epigenetic therapy. More accurate biomarkers are needed to better identify patients who may or may not benefit from intensive chemotherapy. In younger adults, molecular profiling of aberrations such as *NPM1* and *DNMT3A* mutations and *MLL* translocations could identify patients who are most likely to benefit from a certain treatment or dose intensity [57, 58]. However, in multiple studies, patients aged 60 years and older with *NPM1*-mutated AML have far superior outcomes and survival after intensive therapy compared with any other treatment modality [59–61]. Presence of the *FLT3* mutation was associated with a worse outcome, regardless of *NPM1* status [62]. In order to avoid toxicities, hematologists should collaborate more and more with geriatricians to identify clues of vulnerability in elderly patients through the study of functional physical, physiological, cognitive, social and psychological parameters [63]. It appears that chronological age may not be a robust predictor of outcome after accounting for function, comorbidities, and symptoms [64]. These comprehensive geriatric assessments were shown more specific than the screening tool G8, which is the most studied screening tool applied in geriatric oncology [65]. Indeed, systematic measurement of patient-specific factors can help discriminate among fit, vulnerable, and frail patients for a given treatment. Studies have shown that assessment of self-reported activities of daily living and measured physical performance are predictive of survival after accounting for performance status [66, 67]. Better understanding of specific patient vulnerabilities are under evaluation and may help to defined adaptive clinical trial design for specific patient subgroups [68, 69]. The Townsend index, which measures material deprivation based on unemployment, car ownership, home ownership and overcrowding, was found to be significantly increased in older patients and correlated with survival [70]. Furthermore, a correlation has recently been confirmed between the use of potentially inappropriate medication, polypharmacy (defined as the concurrent use of an excessive number of drugs), and increased comorbidities [71]. Polypharmacy should therefore be a critical component of geriatric evaluation [72]. An important issue remains the lack of a prospective definition of the so called ‘unfit’ population. Hypomethylating agents or low-dose cytarabine can serve as backbone low-intensity treatments with which novel therapies could be combined. Decision-making should be determined through patient-centered discussions and taken with the aim to keep an accurate balance between efficacy of therapy and avoidance of a decreased quality of life and loss of autonomy feared by elderly patients and their families. Inclusion in clinical trials will furnish some guarantee for quality of treatment,

while offering the opportunity to contribute to therapeutic progress [73].

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